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REVIEW ARTICLE

Medicinal properties of macrofungi

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Abstract. This review highlights the importance to people of some types of wild fungi considered in the context of non-wood forest products. Macrofungi are used both for food and medicine proposes. Substances isolated from the higher Basidiomycetes and Ascomycetes mushrooms express promising immune modulating, antitumor, antiviral, antibacterial and antidiabetic properties. They have been, and are presently, used against cancer in some countries in Far East as well as in the United States of America and Canada. Their useful properties are mainly conferred by biologically-active polysaccharides present in the fruiting bodies and cultured mycelium. A few dozen different polysaccharide antitumor agents have been developed from such species as: *Ganoderma lucidum*, *Lentinus edodes*, *Schizophylum commune*, *Trametes versicolor* and *Inonotus obliquus.* In the review some other fungi and their properties are also described. The information is provided to widen our knowledge of the importance of the organisms that live in forest ecosystems.

Key words: fungal polysaccharides, medicinal mushrooms, antitumor activities

1. Introduction

Medicinal properties of macrofungi (mainly belonging to Basidiomycota) have been known for ages and used. In folk medicine (Hobbs 1995; Wasser, Weis 1999), history of using many different types of fungal extracts demonstrating immunostimulatory, anti-inflammatory and anticancer activity dates back to ancient Japan, China and other countries from the Far East. In many developed countries (United States of America, Israel), scientific achievements from these regions are used to implement complementary therapeutic methods (Wasser 2002).

Some of the best known substances present in fungi showing pharmacological properties (especially anticancer and immunological) are polysaccharides (Ooi, Liu 2000; Wasser 2002; Mordali et al. 2007; Zhang et al. 2007). Polysaccharides or polysaccharide–protein complexes present in fungi have gained the attention of researchers because it is believed that they can inhibit tumour growth enhancing the organism's abilities to defend itself. They are often called as host's defensive potential or biological response modifiers (Leung et al. 2006; Moradali et al. 2007).

Furthermore, these biomacromolecules have the ability of preventing carcinogenesis and tumours metastasis (Guterres et al. 2005; Lee et al. 2005). The mechanism of anticancer influence of polysaccharides is still not fully understood, but what has been found is that they can activate immune cells. They stimulate lymphocyte and macrophage division and synthesis of cytokines (including interleukins, interferons and immunoglobulins directed against cancers antigens) (Wasser 2002; Mordali et al. 2007).

In the 1970s and 1980s, a few anticancer polysaccharides were isolated. These were: lentynian, schizophyllan and polysaccharide–protein complexes (PSK, PSP) obtained from *Lentinus edodes*, *Schizophyllum commune* and *Trametes versicolor* that are very popular in the Far East countries (Mizuno et al. 1995; Ooi et Liu 2000). Widely used as diet and therapy

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supplements, aiding cancer treatment were also PD-glucans present in *Grifola frondosa*, *Sparassis crispa*, *Agaricus blazei* or *Phellinus linteus.* Many reviews dedicated to issues related to anticancer properties of polysaccharides, esp. isolation, biological activity, have been written in the past decade.

The aim of this work is to show the present state of knowledge about fungi polysaccharides used in medicine, mainly in treating cancer.

2. Anticancer compounds present in fungi

These fungi are considered as macrofungi that have a clear, visible carpophores. Taxonomically they belong to classes Basidiomycetes and Ascomycetes, but the majority belong to the former. The knowledge about the real number of macrofungi is still incomplete. Hawksworth (2001) reports that the number is between 14.000 and 22.000. It is estimated that 2000 species can be eaten without harm to health; 700 have scientifically proven medical properties (Wasser 2002). Fungi are a vast and still not fully used source of new applications in pharmacology and medicine, mostly because of the presence of polysaccharides with immunostimulatory and anticancer properties. Biologically active polysaccharides can be found not only in pericarps, but also in in mycelium (pure culture), sclerotes or filtrates (Cheung 2008). Many fungi polysaccharides are found in the form of glucans with different type of glicosid connections; some are real heteroglicans while others are still connected to proteins (Ooi, Liu 2000). Fungal polysaccharides with anticancer properties seem to be connected to the cell wall, built of chitin, cellulose (1→3, 1→6)-β-glucans and (1→3)-α-glucans or polysaccharide–protein complexes such as: galactomann protein and glucuromannan protein (Zhang et al. 2007). However, anticancer properties were not found in chitin (Mizuno et al. 1995).

Due to the chemical structure, polysaccharides can be divided into homo- and heteroglucans. They are the largest group of polysaccharides with anticancer properties. They are supported by many heteroglicans and polysaccharide–protein complexes. In table 1, some isolated from vegetative mycelium or carpophores polysaccharides compounds with anticancer properties are shown.

Polysaccharides demonstrating antitumour activity differ significantly in terms of chemical structure and physical properties. Homopolimer compounds and complex heteropolimers have a wide range of activity. However, it is extremely difficult to carry out the correlation between structure of polysaccharide and the effectiveness in combating sickness. It seems that a significant role in compound activity is played by a type of glicosides bonds (Bohn, BeMiller, 1995). Surenjav et al. (2006) think that β-glucans containing mainly bonds (1→6) have lower activity in combating cancer cells, similar to those of lower molecular weight. The observed natural inconstancy of anticancer polysaccharides and multiplicity of compounds with different chemical structure, such as heteroglicans and compounds heteroglican-protein, have caused that the issue of which structure of polysaccharide decides its anticancer activity is still unsolved.

3. Selected species and description of substances they include and which are used in medicine

Currently, among fungi used in oncology, the most popular are species belonging to the genus *Ganoderma: G. lucidum*, *G. tsugae*, *G. capense* and *G. applanatum*; they are also the best known medicinal fungi in the Far East (Cheung 2008). They contain a number of polysaccharides with anticancer properties: β-glucan, glucu-ronoglican, mannoglucan, other active heteroglicans as well as polysaccharide–protein complexes. Extract from *G. lucidum* which inhibits proliferation of cancer cells is used in the treatment of breast cancer. One of the glucans, marked as LZS-1, gained from spores of *G. lucidum* in experiments conducted on mice, was effective against sarcoma 180 and Lewis lung cancer (Jiang et al. 2004). Polysaccharide isolated from vegetative mycelium *G. lucidum* is the main ingredient of the drug given to animals (experimental phase) ailing from malignant fibroma. The same compound increases phagocytes activity in the human body (Lee et al. 2003).

Studies on the anticancer effect of substances present in *Lentinus edodes* began in the 1970s (Chihara et al. 1970). Isolated β-glucan, called as letinian, in *in vitro* studies did not show direct influence on cancer cells (Wasser 2002). Attempts of chemical modification of water-insoluble compound (α-(1→3)-D-glucan) to a hydrated sulphate proved to have a positive result, and the use of new compound resulted in inhibition of cancer cells proliferation in 52% patients with breast cancer (Zhang, Cheung 2002).

Schizophyllan isolated from *Schizophyllum commune* is similar to letinian in terms of chemical structure and

Table 1. Antitumour polysaccharides from fungi

Polysaccharide	Species of fungus	Literature
Homoglucans		
(1→6)-ß-glucan	*Agaricus blazei,* *A. brasiliensis,* *Lyophyllum decastes,*	Kobayashi et al., 2005; Camelini et al., 2005; Angeli et al., 2006; Ukawaetal., 2000;
(1→3)-ß-glucan	*Agrocybe cylindracea,* *Amanita muscaria,* *Auricularia auricula,* *Collybia dryophila,* *Cordyceps sinensis,* *Flammulina velutipes,* *Ganoderma lucidum,* *Grifora frondosa,* *Heiricium erinaceus,* *Lentinus edodes,* *Phellinus linteus,* *Pleurotus ostreatus,* *Schizophyllum commune,* *Sparassis crispa*	Yoshida et al., 1996; Kiho et al., 1992; Misakiet Kakuta, 1995; Pacheco-Sanchez et al., 2006; Yalin et al., 2005; Smiderle et al., 2006; Han et al., 1995; Kodama et al., 2002; Dong et al., 2006; Surenjav et al., 2005; Kim et al., 1996; Carbonero et al., 2006; Ogawa and Kaburagi, 1982; Ohno et al., 2000;
ß-glucan	*Trametes gibbona,* *Tylopilus felleus,* *Volvariell avolvacea*	Czarneckiet Grzybek, 1995; Grzybek et al., 1990; Kishida et al., 1989;
Heteroglucans		
Mannogalactoglucan	*Agaricus blazei,* *Fomitella fraxinea,* *Pleurotus cornucopiae,* *P. pulmonarius,*	Cho et al., 1999; Cho et al., 1998; Gutierez et al., 1996; Gutierez et al., 1996;
Xsylo-galactoglucan	*Inonotus obliquus*	Mizuno et al., 1999;
Xsylo-glucan	*Pleurotus pulmonarius,* *Polyporus cnfluens*	Gutierez et al., 1996; Mizuno et al., 1992;
Galacto-xyloglucan	*Hericium erinaceus*	Mizuno et al., 1992;
Heteroglycans		
Heterogalactan	*Agaricus bisporus,* *B. blazei,* *Flammulina velutipes,* *Pleurotus erynii,* *P. ostreatus*	Shidaet Sakai, 2004; Shidaet Sakai, 2004; Shidaet Sakai, 2004; Shidaet Sakai, 2004; Shidaet Sakai, 2004;
Fucogalactan	*Hericium erinaceus*	Shida et Sakai, 2004;
Glucogalactan	*Ganoderma tsugae,* *Hericium erinaceus*	Wangetal., 1993; Wang et al., 2004;
Galactomannan	*Collybia maculata*	Lim et al., 2005;
Mannogalactofucan	*Grifola frondosa*	Zhuang et al., 1994;

Polysaccharide	Species of fungus	Literature
Polysaccharide–protein complex		
(1→6)-ß-D-glucan–protein	*Agaricus blazei*	Honget Choi, 2007;
(1→3)-ß-glucan– protein	*Ganoderma tsuage*	Wang et al., 1993;
Proteoglican	*Ganoderma lucidum,* *Pleurotus ostreatus*	Baek et al., 2002;
α-glucan– protein	*Tricholoma matsutake*	Hoshi et al., 2005;
Polysaccharide– protein	*Hebeloma crustuliniforme,* *Phellinus linteus,* *Tricholoma lobayense*	Choet Chung, 1999; Kim et al., 2006; Liu et al., 1996;
Heteroglican– protein	*Grifora frondosa,* *Pleurotus sajor-caju,* *Tremella fuciformis*	Zhuang et al., 1994; Zhuang et al., 1993; Cho et al., 2006.

biological activity as well as anticancer activity (Jong et al. 1991). Schizophyllan restores and increases cellular immunity in the ill organism by activating macrophages (Okazaki et al. 1995). Endopolysaccharide obtained from vegetative mycelium *Inonotus obilquus* works similarly (Kim et al. 2005).

In the case of (1→3)-β-glucans extracted from *Grifola frondosa*, direct cytoxicity against prostate cancer cells was observed. The reduction of cancer cells was particularly high when polysaccharide was enriched with vitamin C (Konno et al. 2002).

α-Glukan, characterised by low molecular weight, isolated from *Pleurotus ostreatus*, has promising properties. This compound showed direct activity by inducing the cells responsible for killing cancer cells resulting in colorectal cancer (Lavi et al. 2006). However, the other heteropolysaccharide-protein complex obtained from fructification had a strong effect of inhibiting the development of leukaemia cancer cells (Wong et al. 2007).

Polysaccharide-protein compounds obtained from *Trametes versicolor* tested *in vitro* and *in vivo* showed direct or indirect cytoxic activity, restricting the growth of cancer cells proliferation in case of leukaemia and breast cancer (Lau et al. 2004). The polysaccharide-protein complex marked as PSK turned out successful in inhibition of cell growth and DNA synthesis of various cancer types, i.e.: leukaemia, sarcoma, breast cancer and liver cancer (Tsukagoshi et al. 1984). Similarly, the compound marked as PSP (polysaccharide-peptide) proved to be active in the inhibition of lung cancer cells, stomach cancer cells and skin cancer cells proliferation (Cui and Chisti 2003). The capability of polysaccharide-protein connections to stimulate the body's immune system to direct cytotoxic activity seems to result from their unique structural characteristics, protein particles and/or specific carbohydrate bindings (Ooi, Liu 2000).

4. Summary

In the last few decades, much attention has been paid to the use of biological substances present in macrofungi in treating, compulsory therapy or as health diet aids. The most attention researchers give is to the possibility of their safe use in prevention and treatment of cancer. Biologically active polysaccharides in fungi can be mostly found in carpophores, mycelium, sclerota and filtrates. One on the most promising features of polysaccharide-protein compounds present in fungi is activity immunostimulating and anticancer. However, the mechanism of this activity is not yet well understood. The opinion that the mentioned compounds interact with the different immunological cells, which can cause cascade transduction of signals responsible for immunological system reaction, finds acceptance. Many from tested macromolecules can also direct, citostatic interact with cancer cells, inhibiting the process of uncontrolled growth and binding cancer cells. It is possible that both types of activity can be complementary.

Immune-stimulating and anticancer properties of fungi polysaccharides are well described but there is a lack of full characteristics of compound activity at the cellular and molecular levels depending on its construction. The understanding of the process of recognition of fungi polysaccharides (especially β-glucan) by immunological cells receptors and transmitted signals activating would increase the possibilities of practical application of these compounds.

The practical use of medical compounds also requires development and availability of appropriate biotechnologies. The most common way to obtain a quality product is mycelial cultures kept on liquid media. This method allows reducing the fungi collection from natural environments as well as controlling the growth of mycelium.

Many mysteries of fungi have not yet been discovered, and the number of studies on acquisition from these new, valuable for medicine compounds still grows, as evidenced in many publications, including the scientific journal *International Journal of Medicinal Mushrooms*, dedicated to this topic.

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